REMARKS

By this amendment claims 6-8 are amended; and claims 9-25 are added. Claims 1-25 are pending. Claims were amended to clarify dependent status. Support for the claim amendments and new claims 9-20 is found in the specification as filed, for example, in the original claims. Support for new claims 21-25 can be found in the specification as filed, for example at pages 15 and 28. No issue of new matter arises. Entry of the amendment and reconsideration and withdrawal of all pending rejections in each of the multiple parts thereof are respectfully requested.

Rejection Under 35 USC §101

Claims 1-8 were again rejected under 35 USC §101 as allegedly lacking patentable utility. Applicants respectfully traverse this rejection.

The basis for this rejection appears in the Office Action at page 4, last 3 lines: "**the specification and the art provide no guidance what relationship multimutated PS1, apoptotic T lymphocytes and Alzheimer's disease have to do with each other such that the claimed non-human mammals can be used.**"

This requirement is improper with respect to the utility requirement. 35 USC §101 recites "any new and useful . . .". Thus any use is sufficient to overcome a 35 USC §101 rejection. Applicants are not required by statute to show the "any use" proposed in a rejection. "Any use" should be as Applicants perceive. Accordingly, Applicants' proposed utility (with no requirement to show utility mandated by the Examiner) is deemed sufficient to meet the statutory standard. The specification describes one such specific and substantial utility proposed by Applicants at pages 5-7:

> The animal model according to the invention is very advantageous because it corresponds to a practical model which is representative of the phenomena of cell death in AD. Indeed, this model exhibits symptoms associates with AD including in particular apoptosis of the cells and oxidative stress and makes it possible, in addition, to measure these symptoms in the cells of renewable peripheral tissues. It should be noted that oxidative stress also manifests itself in the brain of these animals. Renewable peripheral tissues should be understood to mean any tissue exhibiting a renewal of these cells over time. By way of example of renewable peripheral tissue, there may be mentioned the spleen, the liver,

blood and the like. Preferably, the apoptotic phenomenon is measured in blood cells and still more preferably in the lymphocytes. Among the lymphocytes, the T lymphocytes are preferred for the invention.

* * *

Furthermore, the impairments of the metabolism of calcium and of the free radicals which are observed very clearly in this model are similar to the increase in the latent period for the calcium response and the oxidative stress which are observed with Alzheimer patients (Eckert et al., 1997 and 1998), which reinforces the relevance of this model.

The animal model of the present invention permits, e.g., measurement in blood cells, a renewable tissue that is easily and relatively non-invasively obtained from an animal, for modeling effects on nervous tissues: tissues not no easily obtained and not renewable. Use of renewable tissue has an added advantage of permitting multiple measurements from the same organism, thus allowing for longitudinal studies that might not be possible when biopsies of non-renewable tissues are involved. See specification, page 7, lines 4-7. This utility is thus clearly substantial.

It is specific at least because one utility corresponds to "the phenomena of cell death in AD." Thus this utility that is disclosed in the application as filed clearly meets the statutory standard. Reconsideration and withdrawal of this rejection are respectfully requested.

Applicants again reference the Examiner's reliance on the quote from *Lilly*: "a description of what a material does, rather than what it is, usually does not suffice." This still appears to be misapplied. "Utility" relates to "use" or how something is employed. Thus what it *does* would seem an important consideration for describing "utility". Applicants respectfully submit that past patent applications, for example those merely disclosing ESTs, clearly described the composition of each compound (what it is), but because what each compound did was not adequately described 35 USC §101, utility rejections were made. If the Examiner wishes to maintain this aspect of the rejection, Applicants respectfully request a more thorough explanation to aid their understanding.

As stated above "any use" (specific and substantial) meets the standard of the 35 USC §101 utility requirement. The "use" does not have to be an arbitrary use proposed by the Examiner, but can and should be a use Applicants have invented. While the Examiner wishes to

characterize the statutorily adequate use as requiring a "relationship [between] multimutated PS1, apoptotic T lymphocytes, and Alzheimer's disease, Applicants are not statutorily required to justify this use. The use as shown in the application can be used to meet the standard.

The present invention permits measurement in e.g., blood cells, of activities that mirror those of CNS tissue. Obtaining blood cells is much easier than obtaining CNS biopsies. Thus improvement over the art is shown. These blood cells have been modified (through modifying genetic make-up of the organism) to mirror apoptotic events of the CNS. Use of renewable tissue has an advantage of allowing longitudinal studies; use of peripheral renewable tissue has the added advantage of less invasive procedures. The renewable cells of the transgenic animal are modified by multimutating PS1. This genetic manipulation results in a model representative of cell death in AD! Accordingly, a nexus between renewable tissue such as T lymphocytes and events in AD is produced. This nexus serves as a basis for a useful animal model.

Although AD is not a claim element of claim 1, the use satisfying a statutory utility requirement does not have to be claimed. See, for example, 35 USC §112, where the first paragraph sets forth requirements of the specification; requirements relative to the claims first appear at paragraph 2.

The Office Action at page 6, lines 12 and 13 states: "The rejection is maintained because neither the specification nor the art provide any guidance that the claimed animals are a model of Alzheimer's disease". Applicants respectfully assert that this allegation is baseless. Please see the excerpts from the specification, pages 5-7 seen above. In the specification at page 2, second paragraph, line 1. "AD" is clearly indicated as an abbreviation for Alzheimer's disease. Thus the specification clearly provides guidance that the claimed animals are a model of Alzheimer's disease. For at least this additional reason, reconsideration and withdrawal of this rejection are respectfully requested.

At page 8, line 12, the Office Action states: "it is unclear whether PS1 comprising 5 mutations triggered apoptosis in the claimed animals". Applicants respectfully submit that this is irrelevant. Pedantic argument of what "triggers" versus what facilitates is not productive. Clearly cells with multimutated PS1 survive to produce multiple copies. Thus an event other than merely having the gene is required for apoptosis. Whether the multimutated PS1 is said to "trigger" or merely results in "increased sensitivity to apoptosis" (Specification, page 6, line 20.)

is a distinction not relevant to the rejection at hand. Applicants also wish to clarify that while the discussion raised by the Examiner relates to neurodegenerative disease, the cells of animals of the present invention also exhibit oxidative stress as manifest in the brains of the animals. See, e.g., Example 8. Oxidative stress in brain tissue is another disease trait associated with neurodegenerative disease such as AD. See the specification, for example at page 6, lines 2-6.

The Office Action, at page 8, lines 13 and 14 asserts: 'it is unclear what pathology the claimed animals exhibit such that they are models of T-lymphocyte apoptosis in Alzheimer's disease." Applicants respectfully submit that this is another false requirement. The renewable cells are cells that can be biopsied to assess condition. The model is not one of T lymphocyte behavior, rather renewable cells, such as T lymphocytes, are chosen as models or monitors of other activities such as brain cells that may not be so available. Pathologies as discussed above are specifically mentioned in the application specification, for example, "symptoms associated with AD including in particular apoptosis of the cells and oxidative stress". Page 6, lines 3 and 4. For at least this additional reason, reconsideration and withdrawal of this rejection are respectfully requested.

At pages 8-10, the Office Action asserts a requirement that a specific direct correlation to amyloid plaques be shown. Applicants respectfully submit that this requirement has no sound legal basis. Apoptosis is associated with AD. See citation to Chiu, specification, page 2, last paragraph. Thus an association of the model to apoptosis as exhibited in AD is shown. Metabolism of free radicals, a component of oxidative stress, is shown to be inhibited as expected in the brains of multimutated animals of the invention. Oxidative stress is a known component of AD. See, for example, page 28, lines 9-14. The present model specifically was designed to avoid lengthy experiments previously necessary to observe symptoms of AD. The model is not characterized as a model of plaques, thus a requirement to show correlation with such is clearly improper.

The Office Action supports this observation at page 10, discussing that definitive diagnosis requires observation of neuritic plaques. If Alzheimer's disease were only manifest after death, there would be little concern. The lesson is that other symptoms are associated with AD and deterioration or amelioration of these symptoms can be observed before death. For at least this additional reason, reconsideration and withdrawal of this rejection are respectfully requested.

Further evidence of nexus between AD and cells having mutated presenilin, e.g., PS1, is found in the specification, for example, at page 2, first paragraph. Mutations in this gene are associated with plaques and with other characteristics *inter alia* apoptosis and oxidative stress. Thus mutated renewable cells evidencing such correlated characteristics are useful as surrogates for other cells in the organism, so as to avoid a need to sacrifice animals to study pathology. See specification, page 3, first paragraph. For at least this additional reason, reconsideration and withdrawal of this rejection are respectfully requested.

In view of the above comments, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §101 utility rejection.

Rejections Under 35 U.S.C. §112

Claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection. New issues were raised by the Examiner in response to Applicants previous replies. These and other bases for rejections are discussed below.

The Office Action at page 11, one basis of rejection appears to be an alleged lack of guidance that the mice of the examples that the mice exhibit neurodegeneration associated with AD. Lines 14 and 15. A single aspect of AD is selected as a basis for this rejection. Applicants respectfully submit that enablement rests on a requirement for undue experimentation. Lack of any particular guidance is not demonstrative of a requirement for undue experimentation unless that guidance can be shown both to be lacking and necessary to avoid undue experimentation in order to practice the claimed invention. The animals of the present invention demonstrate cellular impairments which are found in Alzheimer's disease and, in particular, exhibit increased sensitivity to apoptosis. Thus no undue experimentation is required to use animals as claimed as for allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue. See, e.g., page 6, second paragraph:

> Thus, the results described in the examples demonstrate that the transgenic mouse expressing the multimutated PS1 develops cellular impairments which are found in Alzheimer's disease and, in particular, exhibits increased sensitivity to apoptosis.

At page 12 the Office Action appears to propose additional basis for this rejection:

> The issue becomes even less clear in light of the fact that the mice described in the specification are not described to have any neurodegeneration.
>
> * * *
>
> As such, because the specification and the art provide no guidance between the relationship between multimutated PS1 and T lymphocyte apoptosis, the mouse described in the specification is not a model of a human condition and thus, the purported use of the mouse is not readily apparent.

However, mice of the specification have been shown to possess mutations associated with a neurodegenerative disease in humans and that these mutations results in measurable events also known to be associated with neurodegenerative disease. Furthermore, the mutations known to be associated with characteristics such as apoptosis in neurodegenerative disease are also shown to be associated with apoptosis in T lymphocytes of the same animals with the human FAD associated neurodegenerative disease. The mouse or other animal of the present invention is thus clearly a model for characteristics of the neurodegenerative disease found in humans. Use of the mouse as a model is therefore apparent. Accordingly, no undue experimentation is required to use animals of the present invention as a model for human disease.

In the paragraph bridging pages 12 and 13 the Office Action proposes another basis in support of this rejection. Again no issue of undue experimentation is specified.

The Office Action comments that the art is aware that a mutated form of PS1 behaves in a different manner than the wild type. This is not at all surprising since the mutated PS1 is associated with AD. The mutated and wild type proteins are therefore expected to have different characteristics. The Office Action comments that "it is unclear what biological function (if any) PS1M5 has such that apoptosis occurs in T lymphocytes." Applicants respectfully submit that using the present invention without undue experimentation does not require complete understanding of mechanism of action. The Figures clearly demonstrate that the mutation associated with Alzheimer's produces a measurable effect that can be used to monitor characteristics associated with neurodegenerative disease such as AD in renewable tissues such as T lymphocytes. The specification provides guidance on monitoring responses in these cells. Thus no undue experimentation is required. The claims are therefore enabled.

At page 13, the Examiner provides reasoning essentially relying on disbelief of an evidentiary document. A declaration was filed wherein Applicants declared that they each

believed the statements of the specification to be true. Penalties under 18 USC §1001 are specifically acknowledged. Accordingly, citation to the specification is no mere assertion. It must be treated as evidence. The rejection accordingly is clearly improper. Reconsideration and withdrawal of this rejection are respectfully requested.

Another basis of rejection is based on speculation outside the claimed subject matter. The Examiner alleges that one can not reasonably predict that expression of any transgene "necessarily means the phenotype exhibited by the animal is related to the transgene." First, any transgene is not at issue. The claims related to multimutated PS1. Furthermore, enablement relates to "undue experimentation." Absolute certainty is not a requirement. Auerbach is cited for teaching a caveat that insertional mutation and/or differences in genetic background may have an effect. But Auerbach also suggests means to mitigate or to avoid these issues. Most of page 24, column 2 is about maintaining colonies. While stable colonies may be advantageous, they are not necessary to practice the claimed invention. For example, pages 15 and 16 of the specification provide specific guidance for producing animals of the invention. See also Example 1. Multiple mice were used. Thus insertional mutations are unlikely to be the cause of the observed characteristics, especially since the observed characteristics match those known to be associated with the mutated gene. Thus theoretical unpredictability is overcome by the evidence of the specification and cannot properly be said to rise to any level requiring undue experimentation. No issue requiring undue experimentation is here apparent. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The Office Action asserts: "According to the art, an artisan cannot reasonably predict that the components that comprise the transgene construct necessarily work in various species of animals." [Emphasis added.] Once again the wrong standard is used. The standard for enablement is whether undue experimentation is required, not certainty of outcome. A difference was noted by the examiner in recapitulation of a human disease in rats and mice. According to the reference experiments were performed that on their face do not appear to have been undue. The Office Action presents no evidence that reference articles cited in this rejection teach or suggest in any way that undue experimentation would be required to practice the invention. Similarly, for promoters, many are known in the art. Skilled artisans are capable of selecting one or more promoters and may as routine practice use multiple promoters in order to optimize output for the intended purpose. Any person skilled in the art would agree that

selection of a working promoter is routine and cannot be properly characterized as a process necessitating undue experimentation.

At paragraph 16 another aspect of the rejection is summarized as: "it is unclear that the mice described in the specification necessarily exhibit apoptotic lymphocytes because of the transgene or because of unrelated factors (e.g., genetic background and/or the PS1M5 inducing non-specific biological activity) which result in mice that exhibit this particular phenotype." As a first point Applicants respectfully assert that this may be in fact irrelevant. Phenotypic activity matches that known to be associated with the mutated gene in humans. Thus based on phenotype the mice of the examples can serve as models of disease associated with the mutation. Secondly, again no issue of undue experimentation is apparent. Certainty is not a requirement of patent law or even science. Pedantic argument whether something "necessarily exhibits", "most likely exhibits", "probably exhibits", etc., is not necessary to decide the issue of whether undue experimentation is required in order to practice the instantly claimed invention. Since no requirement for undue experimentation is alleged or can be found in this anecdote, this aspect of the rejection does not properly serve as basis for the rejection. Reconsideration and withdrawal of this rejection are respectfully requested.

At the paragraph bridging pages 16 and 17, chemical compounds which differ radically in their properties are mentioned anecdotally as evidence "the specification does not teach how to arrive at apoptosis in other renewable peripheral tissue such as blood." Applicants respectfully submit that aspect of the rejection appears based on a faulty assessment of the skills of the skilled artisan. T lymphocytes are a blood cell! The skilled artisan would also be aware that some components of blood, such as red blood cells and platelets do not have nuclei and therefore cannot initiate apoptosis. No requirement for undue experimentation can properly be asserted here. Other blood cells such as B lymphocytes share the same stem cells, erythropoietic stem cells, as T lymphocytes. Thus the any conclusion that blood cells differ radically in their properties must be qualified or considered suspect. The chemical anecdote of the Office Action thus can not be considered instructive in the present situation. Furthermore, similar properties were shown in brain cells, cells quite different for the T lymphocytes. These major differences are illustrative that the characteristics observed from the mutated T lymphocytes are not specific to the lymphocytes but are found in a variety of cells. In any case undue experimentation would not be invoked for selecting and testing cells for the desired phenotypic expression. Thus well

settled law relating to radically different chemical compounds does not properly apply here. No issue of required undue experimentation is apparent. Reconsideration and withdrawal of this rejection are respectfully requested.

Finally, in the paragraph bridging pages 17 and 18, a final basis for this 35 USC §112 rejection is proposed. The Office Action attempts to support the rejection by opening the discussion with neurodegenerative diseases. The discussion then shifts to Alzheimer's disease. The Office Action argues that Applicants citation of the specification teachings that relate a multimutated PS1 to Alzheimer's disease because "the specification does not provide guidance that the protein recapitulates symptoms associated with the disease such as neuritic plaques." Applicants respectfully submit that this rejection is improper.

The specification provides guidance showing relevance relative to Alzheimer's disease. See, e.g., Example 8. Metabolism of free radicals, apoptosis and Ca^{++} mobilization, are associated with the transgenic animals and Alzheimer's disease. Applicants respectfully submit that at least this portion of the specification shows the mutated protein has relevance to "symptoms associated with the disease such as neuritic plaques." While neuritic plaques are not shown, other symptoms related to Alzheimer's disease are shown. Applicants respectfully submit that these meet the "such as" criterion proposed by the Examiner.

Closing Remarks

Moreover, with general respect to the utility rejection and this enablement rejection, Claim 1 recites:

> 1. Transgenic mammalian non-human animal expressing a multimutated form of presenilin 1 and allowing an apoptotic phenomenon to be detected in a renewable peripheral tissue.

The specification shows how to make the transgenic animal expressing the multimutated PS1. See, e.g., materials and methods, part 2. Examples show that apoptosis and other Alzheimer's disease related phenomena are measurable in peripheral (as well as brain tissue) of these transgenic animals. No undue experimentation is required or has been alleged in the Office Action. Thus this enablement rejection in the Office Action is without foundation. The claims do not recite measuring plaques as the Examiner wishes to require. However, Applicants invention is a model useful e.g., for monitoring effects of exogenous compounds on symptoms

associated with Alzheimer's disease. The model allows easy monitoring of some symptoms because renewable tissue such as blood can be repeatably measured if desired. This model was designed specifically to avoid the need to lay open the brains of animals during necropsy. Plaques appear in brain tissue and are but one symptom of Alzheimer's disease. Applicants have advantageously made use of other symptoms that can be assayed in more easily obtained renewable tissue as a model for Alzheimer's disease. Thus utility and enablement are apparent.

Claims 6-8 are amended above to clarify dependency. Claims 9-20 are added in single dependent form to replace subject matter of claims that previously recited multiple dependency. New claims 21-25 are added to add recitation to dependent subject matter supported in the specification and to emphasize that neurodegenerative disorders include disorders that are not plaque formations.

Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance and request prompt issuance of a Notice of Allowance. Should the Examiner wish to suggest additional changes that might put the application in even better condition for allowance, the Examiner is requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized to charge any fee required for added claims and any additional fees that may be needed to Deposit Account No. 18-1982.

Respectfully submitted,

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